

# Introduction

## Prospective and Retrospective on Cell Biology of the Axon

Axons from projection macroneurons are elaborated early during neurogenesis and comprise the “hard wired” neuroanatomic pathways of the nervous system. They have been the subjects of countless studies from the time that systematic research of the nervous system had its beginnings in the 19th century. Microneurons (i.e., interneurons), which are generated in greater numbers later during neurogenesis, and form local neuronal circuits within functional centers, produce short axons that have not been studied directly, notwithstanding the fact that their sheared-off terminals probably contribute substantially to the heterogeneity of brain synaptosome fractions. Strictly speaking, therefore, for purposes of this volume, axons from projection neurons serve as the principal frame of reference.

In many instances, the mass of a projection neuron’s axon can dwarf the mass of the cell of origin. This consideration, among others, has historically posed questions about the biology of the axon, not the least vexing of which have centered on the basis of axonal growth and steady state maintenance. A simple view has long prevailed until recently, in which the axon was regarded as to have essentially no intrinsic capacity to synthesize proteins. By default, structural and metabolic needs were assumed to be effectively satisfied by constant bidirectional trafficking between the cell body and the axon of organelles, cytoskeletal polymers, and requisite proteins. From this general premise, it was assumed that directed growth of axons in response to guidance cues during development was also governed solely by the cell body. Such a restricted view has been discredited in recent years by a significant body of research that has revealed a considerable complexity governing the local expression *within* axons, which has rendered the traditional conceptual model anachronistic. Many distinctive features and recent research developments that characterize the newfound complexity of the cell biology of axons – a complexity that has clear implications for pathobiology – are reviewed and discussed in the present volume, briefly highlighted as follows.

The first chapter by Thaxton and Bhat reviews the current understanding of signaling interactions and mechanisms that underlie myelination, while also governing differentiation of regional axonal domains, and further discusses domain disorganization in the context of demyelinating diseases.

The following three chapters focus on endogenous cytoskeletal systems that structurally organize the axon, confer tensile strength, and mediate intracellular

transport and growth cone motility. Specifically, Shea et al. address issues of how organizational dynamics of neurofilaments are regulated, including mechanisms of transport, and how dysregulation of transport can contribute to motor neuron disease. Fainikar and Baas focus on organizational and functional roles of the microtubule array in axons and further consider mechanisms that regulate microtubule assembly and disassembly, which, when impaired, predispose axons to degenerate. Letourneau then reviews the characteristics of the actin cytoskeleton, including its organization and functions in mature and growing axons, regulated by actin-binding proteins, and the roles the latter play in transport processes and growth dynamics.

The next set of four chapters deals with selected aspects of intracellular transport systems in axons. Thus, Bridgman identifies several classes of myosin motor proteins intrinsic to the axon compartment and discusses their principal roles in the transport of specific types of cargoes, and in potential dynamic and static tethering functions related to vesicular and translational machinery components, respectively. Zinsmaier et al. review mitochondrial transport and relevant motor proteins, discussing functional imperatives and mechanisms that govern mitochondrial transport dynamics and directional delivery to specifically targeted sites. The following chapter about NGF transport by Campenot provides a critical discussion of mechanisms that mediate retrograde signaling associated with NGF's role in trophic-dependent neuronal survival. In the last chapter of this series, Roy discusses potential impairment of transport and/or subcellular targeting of  $\alpha$ -synuclein that may account for accumulations of Lewy body inclusions in a number of neurodegenerative diseases characterized as synucleinopathies.

The succeeding series of five chapters center on historically controversial areas related to axonal protein synthesizing machinery and various aspects of how local expression of proteins are regulated in axons. The lead-off chapter by Koenig describes the occurrence and organizational attributes of discrete ribosome-containing domains that are identified in the cortex as intermittently spaced plaque-like structures in myelinated axons, and, while absent as such in the unmyelinated squid giant axon, appear as occasional discrete ribosomal structural aggregates within axoplasm. Next, Vuppalanchi et al. present an in-depth review of endogenous mRNAs, classes of proteins translated locally, and discussion of the intriguing and rapidly expanding area of ribonucleoprotein (RNP) trafficking in axons. This is followed with a chapter by Kaplan et al. which provides insight into the importance that local synthesis of nuclear encoded mitochondrial proteins plays in mitochondrial function and maintenance, as well as axon survival. In the following chapter by Crispino et al., evidence is reviewed that supports the occurrence of transcellular trafficking of RNA from glial cells to axons and further discusses the significance that glial RNA transcripts may play in contributing to local expression of proteins in the axon and axon terminals. A chapter by Yoon et al. examines RNA trafficking and localization of transcripts in growth cones and reviews the evidence that extracellular cues modulate directional elongation associated with axonal pathfinding through signaling pathways that regulate local synthesis of proteins. The final chapter of this set by Rossoll and Bassell addresses key genetic and molecular defects that underlie spinal muscular atrophy, a degenerative condition that especially affects

$\alpha$ -motoneurons, and the roles the unaffected SMN gene product plays as a molecular chaperone involved in mRNA transport and translation in axons.

The final two chapters deal with neural responses to axon injury. Ben-Yaakov and Fainzilber review and discuss current understanding about how a local reaction to injury in axons triggers local protein synthesis of a protein that forms a signaling complex, which is then conveyed from the lesion site to the cell body to initiate regeneration. Lastly, Huebner and Strittmatter provide a review and discussion of recent developments in the current understanding of endogenous and exogenous factors that condition axonal regenerative capacity in the peripheral and central nervous systems and identify injury-induced activation of specific genes that govern regenerative activities.

Along with a cursory prospective of the current volume, it seems only fitting to highlight some of the early key antecedents that have led to recent developments in the field. The retrospective begins with selected neurohistologists of yesteryear, who initially established a cellular orientation in the context of nervous system organization and also framed significant issues related to axonal biology in the idiosyncratic language of the late 19th century. Although eclipsed after the turn of the century, the same issues reemerged many years later, when they were reframed in terms of contemporary cell biology. Also given some deserved consideration is the role large-sized axon models played to help advance early investigative efforts at a cellular level.

In his exhaustively documented to me, entitled *The Nervous System and its Constituent Neurones* (1899), Lewellys Barker credits Otto Deiters' descriptions of carefully hand-dissected nerve cells from animal and human brains and spinal cords, published posthumously in 1865, with identifying the distinctive characteristics of the "axone" among multiple neuronal processes. He observed that the "...axis-cylinder ... consist(s) of a rigid hyaline, more resistant substance, which at short distance from its origin in the nerve cell passed directly over into a medullated nerve fibre." Illustrations based on Deiters' deft manual isolation of nerve cells were informative and insightful, but there were fundamentally different concepts competing for acceptance at the time about the underlying functional organization of the nervous system, one of which centered on the notion of a continuous reticular fibrillar network. Conclusive evidence that firmly established the "neurone doctrine" as the basis was ultimately achieved in the last decade of the century, in which the Golgi silver impregnation method to stain neural tissue so aptly employed by Ramón y Cajal in his classical studies, played a key role. Deiters, nonetheless, focused attention on two important axonal features of a major class of projection neurons; namely, mechanical tensile strength, and the myelin sheath investment.

The contemporaneous classical degeneration studies performed on peripheral sensory and motor spinal nerve root fibers by Waller in 1850, and on CNS pyramidal track fibers by Türck in 1852 set the stage for research developments in cellular neurobiology for many years to come. The results made it clear that axons were dependent on cell bodies for structural integrity and viability, which gave rise to the concept of cell bodies as indispensable "trophic" centers. The overriding issue thereby became: How does the cell body actually perform its trophic function?

In attempting to address the conundrum of trophic influence at the turn of the 19th century, Barker (1899) posed the following rhetorical question: “**Does the axon actually receive all its nutrient material from the ganglion cell, or does it depend**, as would seem a priori much more likely, for the most part **upon autochthonous metabolism** needing only the influence of the cell to which it is connected to govern assimilation?” Barker then takes note of “... a very ingenious hypothesis” advanced by Goldscheider; namely, “...that it is most probable that there is an actual transport of a material perhaps a *fermentlike substance* [i.e., enzyme] from the cell along the whole course of the axone to its extremity, and that first through the influence of the chemical body the axone is enabled to make use for its nutrition of the material placed at its disposal in its anatomical course.”

With these two explanations (see bold print above), Barker, in effect, articulated two potential modes of supplying proteins to the axon compartment well before the two corresponding lines of basic research on “local synthesis” and “axoplasmic transport” took root in the mid-20th century. These research foci and their offshoots over the years have yielded a large body of information about the biology of the axon, although, not without controversies along the way.

The era of axoplasmic transport research was ushered in by Paul Weiss’ “nerve damming” experiments in the mid-1940s. Placement of an arterial cuff around a peripheral nerve, whether crushed, uncrushed, or regenerating, produced axoplasmic damming, which resulted in various forms of ballooning, telescoping, coiling, and beading of axons proximal to the compression site. Subsequent release of compression yielded a distal redistribution characterized as a continuous proximo-distal movement of axoplasm at a rate estimated to be about 2 mm/day (Weiss and Hiscoe, 1948). Actually, it was a few years earlier at a Marine Biological Laboratory meeting in Woods Hole that Weiss (1944) first invoked the concept of axoplasmic transport, not only to explain the experimental damming results, but also to suggest it as a general mechanism to account for natural growth and renewal of the axon, which was stated as follows. “*The neuron, as a living cell, is in a state of constant reconstitution. The synthesis of its protoplasm would be confined to the territory near the nucleus (perikaryon). New substance would constantly be added to the nerve processes from their base. The normal fiber caliber permits unimpeded advance of this mass, with central synthesis and peripheral destruction in balance. Any reduction of caliber impedes proximo-distal progress of the column and thus leads to its damming up, coiling, etc.*”

Several reports appeared in the literature during the ensuing decade that supported the idea of axoplasmic transport. While studying the systemic uptake of [ $^{32}\text{P}$ ] into cellular constituents of neurons, Samuels et al. (1951) observed movement of radiolabeled phosphoproteins along nerves at a rate of about 3 mm/day. Lubinska (1954) noted two asymmetrical bulbous enlargements juxtaposed to nodes of Ranvier on each side when examining dissected isolated axon segments, in which the larger of the two was invariably located on the central side of a node. Extrapolating from the cuff compression experiments of Weiss, Lubinska inferred that such perinodal asymmetry was probably caused by the natural constriction of the node that would presumably impede proximo-distal movement of axoplasm.

Studies of neurosecretory neurons in vegetative nervous centers also strongly suggested the transport of neurosecretory material from sites of synthesis in cell bodies to sites of secretion in axon terminals (Scharrer and Scharrer, 1954), while microscopic observations of neurons in culture directly revealed bidirectional movements of axonal granules and vesicular structures (Hughes, 1953; Hild, 1954). Later, the first preliminary report of axoplasmic transport of radiolabeled proteins in cats appeared, based on intrathecal injections of [ $^{14}\text{C}$ ]methionine and [ $^{14}\text{C}$ ]glycine, in which 1–3 cm radiolabeled protein “peaks” “moved” along peripheral nerves at rates of 4–5 mm/day, and 7–11 mm/day (Koenig, 1958).

In the next two decades, more than thousand papers on axoplasmic transport appeared (see Grafstein and Forman, 1980). In advance of the vast growth in the transport literature, Goldscheider’s hypothesis, positing transport of a “fermentlike substance” from the cell body into the axon, was tested in the case of acetylcholinesterase (AChE), a peripheral membrane enzyme in cholinergic neurons anchored to plasma and cytomembranes. Most AChE in neural and muscle tissues was inhibited irreversibly by alkyl phosphorylation of the active center, using diisopropylfluorophosphate (DFP), and recovery of enzymic activity, regarded as an indirect measure of resynthesis, was evaluated along several peripheral nerves and cognate nerve cell centers over time (Koenig and Koelle, 1960). AChE activity reappeared along peripheral nerves and in cell bodies analyzed in manners that were temporally and spatially independent. The findings suggested the likelihood of *local synthesis* in axons as a possible mechanism for enzymic recovery, but did not rule out axoplasmic transport as an alternate, or ancillary mechanism.

In the late 19th century, a basophilic “stainable substance” in nerve cell bodies was revealed by the so-called “method of Nissl” that employed a basic aniline dye to stain nerve cells in neural tissue. The significance of cytoplasmic Nissl substance/Nissl bodies was eventually elucidated with the advent of electron microscopy (EM), when basophilic aggregates were identified as ribosome-studded, rough endoplasmic reticulum (Palay and Palade, 1955). Palay and Palade also noted in their EM survey of the nervous system that while ribosomes were apparently absent from mature axons, they were present in dendrites, and that nerve cell bodies were richly endowed with ribosomes much like gland cells. The long recognized lack of Nissl staining in the axon hillock region (the funnel-like protuberance arising from the perikaryon) and initial segment became recognized as a characteristic hallmark of axons. Moreover, nerve cell bodies were thought to have more than sufficient capacity to synthesize and supply requisite proteins via axoplasmic transport to support growth and maintain mass of an extended axonal process. Nonetheless, negative results based on randomly selected thin sections viewed at an ultrastructural level could not be considered necessarily conclusive. The uncertainty issue made the corollary question of whether axons contained RNA compelling to answer.

During the mid-1950s, RNA distribution was investigated in immature neurons during development of the chick spinal cord (Hughes, 1955), and the guinea pig fetal cerebral cortex (Hughes and Flexner, 1956), using a microscope equipped with quartz optics, and a UV light source in a spectral region selective for RNA absorption. Ultraviolet microscopy revealed that RNA was diffusely distributed within

immature axons, but then disappeared just before Nissl bodies formed in cell bodies. Efforts to investigate RNA, or endogenous protein synthesizing activity directly in the *mature* axon, however, was not possible until sensitive quantitative methods of detection and analysis at a cellular level were developed, including the availability of a suitable axon model.

Axon models played important roles in early studies at a cellular level, not only initially to investigate axonal electrophysiology, but also later to analyze axonal RNA, and rheological properties of axoplasm. The squid giant axon was the first experimental model to be employed for the purpose of intracellular electrophysiological recording. Its use by Hodgkin and Huxley (1939) made it possible to document the reversal of membrane polarity during the overshoot of an action potential. The findings refuted the Bernstein theory that prevailed since the turn of the 20th century, which predicted that an action potential would simply cause the negatively polarized membrane to collapse to 0 mV. The landmark experiment entailed inserting an electrode axially into a squid axon that was 500  $\mu\text{m}$  in diameter, dissected from *Loligo pealeii*. Also, importantly, the experiments established for the first time the existence of a functional plasma membrane.

It is especially noteworthy that Hodgkin and Huxley acknowledged the English zoologist, anatomist, and neurobiologist, J.Z. Young, who had discovered the giant axon a few years earlier, for having recommended its use. Later, Young (1945) conjectured that axoplasm is a viscous fluid that is likely to exhibit non-Newtonian flow behavior, a property in which stress force produces nonlinear flow (e.g., initially resisting flow, but then finally yielding to flow at a critical force, with flow accelerating thereafter). Young drew his inference about non-Newtonian flow behavior on the basis of weak form birefringence of axoplasm shown by inspection in polarization microscopy. The form birefringence was attributed to the “neurofibrillar” organization of axoplasm.

The conjecture was later confirmed in Robert Allen’s laboratory, at which time a rheological model was formulated as a result of experiments in living squid axon preparations. Specifically, in addition to showing that axoplasm was firmly attached to the plasma membrane and that it could be easily sheared, axoplasm was characterized as a “complex viscoelastic fluid”, having an elastic modulus greater in the longitudinal direction than in the radial direction (Sato et al., 1984). Such rheological behavior is consistent with our present understanding of how the three major cytoskeletal systems are organized and interact in the axon; i.e., linearly oriented structural elements, comprising microtubules (e.g., see Fainikar and Baas, this volume) and neurofilaments that exhibit lateral crossbridging (e.g., see chapter by Shea et al., this volume), in addition to a diffuse actin filament network, which in part also forms a dense cortical layer, consisting of a submembraneous F-actin network, essential for membrane stability and anchoring many integral membrane proteins (e.g., see Letourneau, this volume).

The visco-elastic properties of axoplasm made it possible to extrude axoplasm out of a cut end of squid giant fibers, much like expressing toothpaste from a tube. On the other hand, its quasi solid-like properties also made it feasible to translate axoplasm out of its myelin sheath with microweezers as an “axoplasmic whole-



mount” (e.g., see Koenig, this volume). Indeed, the tensile strength and ease with which axoplasm can be translated as a whole-mount are enhanced with an increase in axon diameter due to the corresponding greater neurofilament content.

Allen also greatly advanced in research in the field of axoplasmic transport with the development of *video enhanced differential interference contrast microscopy*, which made it possible to visualize organelles transported along microtubules at a submicroscopic level in the squid giant axon (Allen et al., 1982), and in extruded axoplasm (Brady et al., 1982). The methodological approach was key to the subsequent discovery of kinesin (Vale et al., 1985), the first of a number of microtubule, and F-actin dependent molecular motor proteins later characterized.

The vertebrate’s equivalent to the squid giant axon model is the large, heavily myelinated Mauthner axon in goldfish, and in other teleost fishes. While it is not at par with the squid axon with respect to size, it is exceptionally large for a vertebrate axon, in which the axoplasmic core can range from 20 to 90  $\mu\text{m}$  in diameter. The paired axons originate from very large, electrophysiologically identifiable Mauthner nerve cells located in the hindbrain. The rapidly conducting Mauthner axons project the length of the spinal cord, giving off very short collaterals through the myelin sheath (e.g., see Koenig, this volume), which synapse with a neuronal network that triggers a “C-bend” reflex of the trunk musculature to initiate an escape response.

In the late 1950s, Jan-Erik Edström developed ultramicro analytic methods for RNA in the picogram range designed for isolated microscopic samples. The possibility that axons may have an intrinsic capacity to synthesize proteins (Koenig and Koelle, 1960), notwithstanding an apparent lack of ribosomes (Palay and Palade, 1955), prompted Edström et al. (1962) to analyze RNA extracted by ribonuclease digestion of isolated axoplasm micro-dissected from fixed goldfish Mauthner cell fibers. The landmark study, and subsequent analysis of axoplasm from Mauthner (Edström, 1964a; 1964b), and spinal accessory fibers of the cat (Koenig, 1965), documented the occurrence of RNA in adult vertebrate axons, and provided the first quantitative data about RNA content and nucleotide base composition. More than a decade elapsed before ribosomal RNA (rRNA) was demonstrated in axoplasm isolated from Mauthner fibers (Koenig, 1979), and unmyelinated squid giant fibers (Giuditta et al., 1980). Eventually, a systematic cortical distribution of novel ribosome-containing structural domains was revealed in isolated vertebrate axoplasmic whole-mounts (Koenig and Martin, 1996; Koenig et al., 2000), while in the squid giant axon, ribosomes were observed to be clustered in randomly distributed structural aggregates within the core of axoplasm (Martin et al., 1998; Bleher and Martin, 2001) (e.g., see Koenig, this volume).

Evidence of local protein synthesis and translational machinery in axons has long been held captive by the sway of the deeply ingrained view in neurobiology that axoplasmic transport is the sole source of all axonal proteins. Such a view was promulgated in early literature, and, later, reinforced periodically by dogmatic assertions in reviews of axoplasmic transport, illustrated, for example, by the following: “*Remarkably, synthesis of all axonal proteins is restricted to a cell body tens of micrometres in diameter. Every protein has to be transported from where it is made to where it is needed*” (Brady, 2000).

To the contrary, a newfound complexity, which is recognized and documented in the present volume, controverts long held shibboleths regarding the single mode of expression in axons. There are now clearly strong reasons for adopting a balanced, broadly based view about gene expression vis-à-vis axons of projection neurons. Intracellular transport systems not only deliver proteins to axons directly, but also deliver and localize mRNA transcripts for translation as an integral part of RNP-dependent RNA trafficking from the soma. In addition, a third source of gene products potentially reaches the axon via a local transcellular route from adjacent ensheathing cells. Differences in contributions of gene products to the axonal compartment from each of these potential sources will likely vary, depending on the specific neuronal phenotype. Differences among the three potential sources are also likely to depend upon the state of the neuron; i.e., during the growth of immature axons, during steady state maintenance and functional activity of mature axons, and during the reaction of axons to injury. Sorting out the relative importance of each source in the various exigency states of the neuron, as well as analyzing the roles that transport systems play on the supply side would not only deepen our understanding of the normal biology of the axon, but should also offer insight into the potential for pathobiological dysfunctions. At this juncture, these quests must be left for future “axonologists” to pursue.

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